Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 40-45 and 47-57 are pending in the application, with claim 40 being the sole independent claim. Claim 46 is sought to be canceled without prejudice to or disclaimer of the subject matter therein. Claim 40 is sought to be amended. Support for the amendment to claim 40 can be found throughout the specification, for example, at paragraph 0099 on page 23, and in claim 7 as originally presented. These changes are believed to introduce no new matter.

I. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 40-46 and 49-57 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. *See* Office Action, page 3. According to the Examiner,

> the specification, while being enabling for a method of converting a large capacity cloning vector into an HSV-based amplicon, wherein the large capacity cloning vector is a plasmid, BAC, PAC, cosmid, YAC or viral-based vector, does not reasonably provide enablement for a method of converting a MAC or human artificial chromosome to an HSV-based amplicon.

See Office Action, pages 3-4. Applicants respectfully traverse this rejection.

Nonetheless, solely to expedite allowance of the application, independent claim 40 has been amended to specify that the large capacity cloning vector is a bacterial artificial chromosome (BAC), P1 phage-based vector (PAC), cosmid, yeast artificial chromosome, or viral-based vector. In light of this amendment, the rejection under § 112, first paragraph, is fully accommodated and should be withdrawn.

II. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 40-46 and 49-57 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. *See* Office Action, page 6. According to the Examiner,

> The claims are indefinite in the recitation of "large capacity cloning vector". The specification does not set forth the metes and bounds of a "large capacity" vector such that the skilled artisan would know how to distinguish a vector that is large capacity from a vector that is not large capacity.

See id. Applicants respectfully traverse this rejection.

Nonetheless, solely to expedite allowance of this application, independent claim 40 has been amended to specify that the large capacity cloning vector is a plasmid, bacterial artificial chromosome (BAC), P1 phage-based vector (PAC), cosmid, yeast artificial chromosome, or viral-based vector. In view of this amendment, the basis for the rejection

under § 112, second paragraph, is moot. Applicants respectfully request that this rejection be reconsidered and withdrawn.

III. Claim Rejections Under 35 U.S.C. § 103

A. Kim in View of Wang and Woodfield

Claims 40-56 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kim *et al.*, *Genome Res. 8*:404-412 (1998) ("Kim") in view of Wang *et al.*, *J. Virol. 70*:8422-8430 (1996) ("Wang") as evidenced by Woodfield *et al.*, *Nucl. Acids. Res. 28*:3323-3331 (2000) ("Woodfield"). *See* Office Action, page 8. Applicants respectfully traverse this rejection.

In order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. *See In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). A showing of combinability of references, in whatever form, must be "clear and particular." *See In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). "Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" *Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617. As discussed below, no evidence has been presented to indicate that a person of ordinary skill in the art would have been motivated to modify or combine the cited references. Thus, a *prima facie* case of obviousness has not been established.

Kim refers to recombining a BAC clone with a DNA construct containing the GFP reporter gene and the *neo* selectable marker gene in order to introduce the GFP and *neo* genes into the BAC. *See* Kim, page 405, left column. Kim does not teach or suggest recombining a BAC with an amplicon vector.

Wang refers to hybrid "miniviral vectors" that contain an HSV-1 origin of DNA replication and an HSV-1 viral packaging sequence. *See* Wang, page 8424, bottom left column. There is no teaching or suggestion in Wang to recombine a miniviral vector with any other genetic construct.

With respect to motivation to combine references, the Examiner asserted that:

> Motivation to combine [Kim and Wang] comes from the nature of the problem to be solved in the method of Kim *et al.*, which is to provide BAC clones comprising genomic DNA inserts with the capacity to transform sufficient numbers of mammalian cells with [sic] for functional analysis of the cloned inserts.

See Office Action, page 10. It is unclear how the Examiner's statement of the nature of the problem to be solved by Kim would have in any way motivated a skilled person to recombine a BAC with an amplicon vector. If the Examiner is correct that the nature of the problem to be solved by Kim is to provide BAC clones comprising genomic DNA inserts with the capacity to transform sufficient numbers of mammalian cells for functional analysis of the cloned inserts, then a person of ordinary skill in the art would have concluded that

Kim has adequately solved this problem and would therefore have had no motivation to combine or modify this reference.

For instance, it is noted in Kim that "[w]e have described a simple and efficient method to modify BAC clones to contain additional genes in the BAC vector." *See* Kim, page 408, sentence bridging left and right columns. It is further noted that "[e]ukaryotic cells that are transfected with a BAC that has been retrofitted with RETRObac are easily identified by FACS analysis or antibiotic selection. These modifications allow for the use of the retrofitted BAC clones as shuttle vectors and increase their utility in functional studies." *See* Kim, page 409, top left column. From the perspective of a skilled person, the experimental results of Kim would have confirmed that the system set forth in this reference had more than adequately solved the problem articulated above by the Examiner.

Figures 3 and 4 on page 409 of Kim show the results of an experiment in which a retrofitted BAC clone expressing GFP (clone "222N15") was transfected into human cells. According to Kim:

> Figure 3 shows the cells 1 week after transfection, viewed using either bright-field or fluorescent microscopy. Visual analysis after 2 days showed that ~10% of the cells were green. FACS analysis was performed to quantitate relative green fluorescence. Figure 4 presents a histogram showing relative fluorescence of SW480 cells transfected with parental BAC DNA or retrofitted BAC DNA. Whereas the parental transfection showed only background levels of green fluorescence (0.13%), cells transfected with

> retrofitted BAC DNA showed 5.73% of the cell population emitting green fluorescence.

See Kim, page 407, right column.

In addition, Figure 5 on page 409 shows the results of an experiment in which murine NIH-3T3 cells were transfected with a retrofitted BAC containing human *p53* genomic DNA. RT-PCR analysis of the transfected cells confirmed expression of the genomic insert. *See* Kim, paragraph bridging pages 407-408.

In view of the experimental results presented throughout Kim, a person of ordinary skill in the art would have concluded that the system set forth therein would satisfactorily provide BAC clones comprising genomic DNA inserts having the capacity to transform sufficient numbers of mammalian cells for functional analysis of the cloned inserts. There would have been no reason for a skilled person to seek to modify or improve the system of Kim in any way and certainly would not have been motivated to use an amplicon vector in the system.

The Examiner, in explaining the obviousness rejection, has emphasized the supposed "inefficiency" and expense associated with transfection using the retrofitted clones of Kim. In particular, the Examiner stated that:

> Kim *et al.* further teaches that the method of introducing the BAC clones into mammalian cells disclosed therein was inefficient (from 1% to 6% transfection efficiency) and required 3 weeks antibiotic selection to obtain stable clones.

See Office Action, page 9. From this interpretation of Kim, the Examiner asserted that motivation to combine Kim and Wang comes from:

> the inefficiency of transfection using BAC vectors retrofit with only selectable markers as taught by Kim *et al.*, which necessitated time consuming and expensive antibiotic selection of transformed cells; and the very high gene transfer efficiency of the amplicon vector of Wang *et al.*, which would allow the skilled artisan to obtain a large number of mammalian cells comprising BAC clones without the need for antibiotic selection.

See Office Action, page 10. Applicants respectfully submit that the Examiner's interpretation of Kim is incorrect and that a person of ordinary skill in the art would not have been motivated to improve the efficiency with which the vectors of Kim are transfected into cells or to reduce the expense associated with antibiotic selection.

First, contrary to the Examiner's assertion, Kim does not "teach[ ] that the method of introducing the BAC clones into mammalian cells disclosed therein was inefficient." Rather, Kim simply notes that "[t]ransfection efficiencies of the modified BACs into human or murine cell lines ranged from 1% to 6%." *See* Kim, Abstract.

Efficiency, in the context of cell transfection, is a relative variable that is dependent upon the particular cells used and the nature of the transfected nucleic acid construct. A transfection efficiency of 1% may in fact be considered very high depending on the

particular cells and nucleic acid constructs used. The particular cell lines used in Kim were SW480 human colorectal cancer cells and murine NIH-3T3 cells, and the retrofitted BAC clones that were used were identified as clones 222N15 and 261M17. *See* Kim, page 407, right column. There is nothing in Kim or in any art of record to indicate that 1% to 6% transfection efficiency of human SW480 cells or murine NIH-3T3 cells with DNA constructs having the characteristics of clones 222N15 and 261M17 would have been regarded as "inefficient" by persons of ordinary skill in the art. In the absence of any such evidence, the rejection cannot be maintained on this basis.

Moreover, it appears from the experimental results presented in Kim that the transfection efficiencies obtained with the retrofitted BAC clones was more than adequate for purposes of detecting and analyzing the expressed transgenes. *See, e.g.*, Kim, Figures 3-5 on page 409.

Furthermore, there is no evidence of record to suggest that antibiotic selection of transfected cells was considered "time consuming and expensive," as asserted by the Examiner. There certainly is nothing to indicate that persons of ordinary skill in the art were seeking to eliminate the use of antibiotic selection altogether as the Examiner's argument requires.

Significantly, the Examiner's assertion that "the amplicon vector of Wang *et al.* . . . would allow the skilled artisan to obtain a large number of mammalian cells comprising BAC clones *without the need for antibiotic selection*," is incorrect. The system of Wang requires that the miniviral vectors be packaged into virions by first transfecting the vectors into E5 mammalian cells, followed by *two to three weeks of antibiotic selection* to obtain

stable, antibiotic resistant colonies. *See* Wang, page 8424, middle right column. Thus, combining Kim and Wang would not have eliminated the need for a two to three week antibiotic selection step. The Examiner's asserted motivation to combine Kim and Wang is therefore based on a factually incorrect premise.

In sum, there is no evidence of record to support the Examiner's assertion that the transfection efficiencies observed with the system of Kim would have been regarded as "inefficient" by persons of ordinary skill in the art. Likewise, there is no evidence of record to support the assertion that persons of ordinary skill in the art were somehow motivated to eliminate the use of antibiotic selection due to cost and time concerns. Furthermore, combining Kim with Wang would not have eliminated the need for an antibiotic selection step in any event since both references require transfection and antibiotic selection steps. Since the asserted motivation to combine references is unsupported by any evidence and is factually flawed, a *prima facie* case of obviousness has not been established. Applicants therefore respectfully request that this rejection be reconsidered and withdrawn.

B. Kim in View of Wang and Saeki

Claims 40, 56 and 57 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kim in view of Wang and further in view of Saeki *et al.*, *Hum. Gene Ther.* *9*:2787-2794 (1998). Applicants respectfully traverse this rejection.

The rationale for this rejection assumes that the subject matter of claims 40 and 56 would have been obvious in view of Kim and Wang. *See* Office Action, page 12. As explained above, a person of ordinary skill in the art would not have been motivated to combine Kim and Wang, and no evidence has been presented to support the Examiner's

assertion of a motivation to combine these references. Therefore, the subject matter of claims 40 and 56 would *not* have been obvious in view of Kim and Wang. Thus, for at least the reasons set forth in section III.A, above, Applicants submit that the obviousness rejection of claims 40, 56 and 57 based on Kim, Wang and Saeki is likewise improper. Applicants respectfully request that this rejection be reconsidered and withdrawn

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and that, as such, the present application is in condition for immediate allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,
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